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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,188	10/15/2001	Avi J. Ashkenazi	GNE.2630P1C8	5212

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,188	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-66 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 58-66 and 68-70 are pending in the instant application. Claim 67 has been canceled and claims 58-66 have been amended as requested by Applicant in the Amendment filed November 18, 2004.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 58-66 and 68-70 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office action, mailed May 19, 2004, at pages 4-8 and below.

Applicants' arguments (pages 15-27, Paper filed Nov. 18, 2004) have been fully considered but are not deemed persuasive.

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Applicants' arguments (pages 15-27, Paper filed Nov. 18, 2004) have been fully considered but are not deemed persuasive.

Applicants traverse the rejection and discuss the legal standard for utility on pages 16-18, and starting on page 18 discuss the proper application of the legal standard. Applicants rely on the gene amplification data for patentable utility for the PRO274 protein, and explain the gene amplification assay of Example 114, in which PRO274 is amplified more than two fold in three types of human primary lung tumors, which Applicants assert is significant and that the PRO274 gene has utility as a diagnostic of lung cancer. Applicants submit a Declaration signed by Dr. Thomas D. Wu, in which he describes 3 sets of microarray experiments in which lung tissue samples from 19 healthy patients and from at least 76 patients having a variety of different types of lung tumors were compared. Dr. Wu found that for each type of lung tumor mentioned at least 10% of the patients with that type of lung tumor have overexpressed levels of PRO270 mRNA in their tissue samples compared to normal lung tissue samples from patients without lung cancer. Dr. Wu states that it is his opinion that when, the mRNA of a gene is overexpressed in at least about 10% of the lung tumors of the same type, the gene is biologically significant as a lung tumor marker, and it is well known in the art that a lung tumor marker that is expressed in each type of lung tumor is very rare.

The Wu Declaration filed under 37 CFR 1.132, filed Nov. 18, 2004 is insufficient to overcome the rejection of claims 58-66 and 68-70 as set forth in the last Office action because: while the declaration provides further support that the mRNA is overexpressed in about 10% of all lung cancers of various different types and could possibly be useful as a cancer marker, the declaration does not provide any information on the extent of overexpression of the PRO274 mRNA, or how significant the overexpression is. It should be noted that the statement on page

19 of the response, lines 5-7, is not accurate with respect to the Wu declaration. On page 19 of the response is written:

> "As stated in the Declaration, Dr. Wu found that for each type of the lung tumors listed above, the mRNA expression level of PR0274 was at least 10% or greater in the lung tumor tissues compared to normal lung tissues."

What the Wu declaration states is that the mRNA is overexpressed in about 10% of all lung cancers of various different types, which is different from that stated above. While the specification provides data that the PRO274 gene is overexpressed in three out of eighteen lung cancers (17%) at a level of two to about three fold over expression in normal lung tissue, the Wu declaration does not provide any information on the degree of overexpression in the cancer samples. For example, is the overexpression 1.5 fold, 2 fold or 5 fold over normal? Without this information the accuracy and significance of the results of the microarrays cannot be adequately assessed.

Applicants also provide the Declaration by Dr. Audrey Goddard, in which she states that a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer. Applicants assert that as the TaqMan realtime PCR method has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification, one of ordinary skill in the art would find it credible that PRO274 is a diagnostic marker of human lung cancer.

The Goddard Declaration filed under 37 CFR 1.132, filed Nov. 18, 2004 is insufficient to overcome the rejection of claims 58-66 and 68-70 as set forth in the last Office action because:

while the declaration and supporting references are convincing that the TaqMan realtime PCR method is very sensitive and can identify amplified genes, the claims are drawn to protein encoded by the PRO247 gene, and as discussed in the previous office action and below, it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production.

Applicant argues that the Gygi et al. publication does not support the rejection. Applicant characterizes Gygi et al. as teaching that there is a general trend but no strong correlation between polypeptide expression level and transcript level. Applicant further characterizes Gygi et al.'s conclusions as showing that there is a positive correlation between transcript and polypeptide for most of the 150 yeast polypeptides studied, but the correlation is not linear and thus one cannot accurately predict polypeptide levels from mRNA levels. Applicant concludes that Gygi et al. show that it is more likely than not that a positive correlation exists between mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO274. There is no evidence regarding whether or not the PRO274 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Since the instant claims are directed to PRO274 **polypeptide**, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Gygi et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that

variances as much as **40-fold** or even **50-fold** were not uncommon. While Gygi et al. demonstrates that **high levels** of mRNA generally correlate with high levels of protein, it has not been demonstrated that the PRO274 mRNA is overexpressed at high levels. The majority of mRNAs at levels of expression other than high levels do not show a correlation with protein levels. Given the small magnitude by which the DNA copy number of PRO274 is increased, and the evidence provided by Gygi et al. and Pennica et al., it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA **or** polypeptide levels, and that it is not more likely than not that a higher level of mRNA correlates with a higher level of protein. One skilled in the art would do further research to determine whether or not the PRO274 polypeptide levels increased significantly in the tumor samples. The requirement for such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases)

chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which are not likely to be in a chromosomal region which is highly amplified, given the low ΔCT values. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO274 in the instant specification. That is, it is not clear whether or not PRO274 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention.

Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO274 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The Polakis declaration under 37 CFR 1.132 filed Nov. 18, 2004 is insufficient to overcome the rejection of claims 58-66 and 68-70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons: In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics, and that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO274 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to

overcome the rejection of claims 58-66 and 68-70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). PRO 274 does not display a 10-fold or greater amplification, according to the specification.

Applicants further assert that even if one assumes that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantially utility, and provides the declaration by Dr. Avi Ashkenazi. Dr. Ashkenazi explains

that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

The Ashkenazi declaration filed under 37 CFR 1.132 filed Nov. 18, 2004 is insufficient to overcome the rejection of claims 58-66 and 68-70 based upon lack of utility as set forth in the last Office action because: it has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician would accordingly decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product.

Applicants provide the Hanna et al. reference to support the Declaration of Dr. Ashkenazi. The Hanna reference is not applicable to the instant fact situation, as it deals with a known tumor associated gene, and not with a prospective analysis of the type found in this specification.

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. For all of these reasons, the rejections are maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 58-66 and 68-70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

4.2 Claims 58-62, 69 and 70 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection and assert that the specification discloses a substantial, specific and credible utility for the PRO274 polypeptide, and have additionally amended claims 58-62 to "wherein the nucleic acid encoding the polypeptide is amplified in lung tumors".

Applicants submit that since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation.

Applicants' arguments have been fully considered but are not deemed persuasive. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are functional, in that the the protein of SEQ ID NO: 7 is encoded by a nucleic acid that is amplified in lung cancer. The specification discloses only a single sequence, SEQ ID NO: 7, that meets the limitations of the claims. It is clear that while there *could* be additional polypeptides that meet the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO: 7 would occur in nature and further be associated with lung cancer. As previously stated, one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQZII 1481 at 1483. In *Fiddes,* claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, applicants have described a single sequence asserted to be associated with lung cancer, and propose to obtain coverage for all related sequences that have a similar association. There is no description of that class of compounds. This case is also analogous to that in *Amgen v. Chugai*, 18 USPQ 2d 1017 (1991), in which it was found that conception may not be achieved until reduction to

practice in cases involving cloning genes. In this case, applicants have no conception of which of the thousands of possible polypeptides and nucleic acids that could encode the protein of SEQ ID NO: 7 would meet the limitation of being amplified in lung cancer.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. Chugai Pharmaceutical Co. L td.*, 18 USPQ2d 1016.

Therefore, polypeptides comprising the sequence set forth in SEQ ID NO: 7, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Rejections over Prior Art

Claim Rejections - 35 USC § 102 and § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5.1 Claims 58-66 and 68 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, for reasons of record in the previous Office Action, mailed May 20, 2004, at page 11, and below.

5.2 Claims 69 and 70 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, in view of Hopp et al., U.S. Patent Number 5,011,912, for reasons of record in the previous Office Action, mailed May 20, 2004, at pages 12-13, and below.

Applicants traverse the rejections and assert that they rely on the gene amplification assay for patentable utility which was first disclosed in International Application NO. PCT/US00/03565, filed Feb. 11, 2000, and assert that they are entitled to at least that filing date, so that Ho et al. is not prior art. Applicants' arguments have been fully considered but are not deemed persuasive, because the gene amplification assay fails to provide a patentable utility for the protein, for reasons discussed above, and the rejections are maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

6. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER